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REMARKS

Claims 1-5, 7, 8, 10-13 and 18-38 stand rejected under 35 U.S.C. §112, second paragraph, as being indefinite. The Examiner states that the term "substituted" in claims 1, 11, 32 and 36 renders the claim indefinite.

Applicants submit that the term "substituted" in relation to 5-substituted-4,6-dichloropyrimidines and 5-substituted-4-chloro-6-hydroxypyrimidines is not indefinite. This objection was not raised against the parent case and a patent was allowed (US 6,608,199) with these terms in the granted claims. In the instant application, the term "substituted is defined in the specification at bottom of page 7 to page 8 where it states:

> In the case where a 5-substituted-4,6-dichlorpyrimidine or a 5-substituted-4-chloro-6-hydroxypyrimidine is formed, the 5 substituent is the same moiety as the R^1 moiety of the above imidoyl chloride.

Further it is stated on page 9:

> If R_1 is other than hydrogen, the method of the invention produces 5-substituted-4,6-dichloropyrimidines. For example, if R_1 is CH_2CH_3, the method of the invention produces 5-ethyl-4,6-dichloropyrimidine.

Applicants therefore submit that the term "substituted" is not indefinite and should remain in claims 1, 11, 32 and 36. One skilled in the art reading the claims would be able to determine the appropriate substituents in light of the disclosure in the specification.

The reasons for rejection cited in paragraphs 2 through 4 of the current office action (pages 2 and 3) have been obviated by the amendment of claims 1, 10, 32 and 36. Withdrawal of the rejections under 35 U.S.C. §112, second paragraph, is respectfully requested.

Claims 1-5, 7, 8, 10-13 and 18-38 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Pavlenko et al. (Russian Journal) in view of Mais et al. (U.S. Patent 6,441,171); and over Glushkov et al. (Russian Journal) in view of Mais et al. (U.S. Patent 6,441,171). The Examiner states that it would have been obvious to modify the method of Mais, by including the cyclization step as taught by Glushkov to attain the advantages of such as disclosed by Glushkov.

Mais describes the preparation of 4,6-dichloropyrimidine by the chlorination of 4-chloro-6-methoxypyrimidine in the presence of a nitrogen-containing auxiliary using phosgene as the chlorinating agent. This reference teaches only that it is possible to

transform the 6-methoxy group of 4-chloro-6-methoxypyrimidine to a 6-chloro group using phosgene in the presence of a nitrogen-containing auxiliary. It teaches nothing about forming 4,6-dichloropyrimidine by an acyclic route.

It is difficult to understand the relevance of the Examiner's comment: "Additionally, Mais teaches that the R group can include C_{1-10} alkyl group". This apparently refers to an R group on the nitrogen-containing auxiliary. The nitrogen-containing auxiliary is used by Mais either as a catalyst (col. 1, lines 55-60) or both as a catalyst and solvent (col. 1, lines 60-63). It has nothing to do with any component of an acyclic preparation, which is what the Examiner seems to be implying.

Pavlenko *et al* describes the cyclization of a single species, *N,N*-dimethyl-*N'*-(1-chloro-2,2-dicyanovinyl)-C-chloroformamidine, to 4,6-dichloro-2-dimethylamino-5-cyanopyrimidine in the presence of a catalyst. Pavlenko does not teach the formation of a 4,6-dichloropyrimidine using two different imidoyl chlorides as required by the process of Applicants' claimed invention.

Even taken together, Mais and Pavlenko *et al* do not teach all the elements of the instant process. It is impossible to construct any obviousness argument from these two references. The Examiner's rejection is therefore fundamentally flawed and should be withdrawn.

Glushkov *et al* does not teach any acyclic preparation of a pyrimidine as suggested by the Examiner. All the pyrimidines prepared by Glushkov *et al* are derived from the ready-formed 4,6-dichloro-5-aminopyrimidine (IV). There being no teaching of an acyclic route to a 4,6-dichloropyrimidne in Glushkov *et al*, the necessary elements of the instant invention are not present in the combined teachings of Mais and Glushkov *et al*, and, again, the Examiner's argument collapses.

For the convenience of the Examiner, Applicants have obtained English versions of the two references and have included them with this Response. The above comments are based on these references.

In view of the above comments, Applicants request withdrawal of the rejections under 35 U.S.C. §112, second paragraph, and 35 U.S.C. §103(a). Early and favourable issuance of a Notice of Allowance for pending claims 1-5, 7, 8, 10-13 and 18-38 is respectfully solicited.

Respectfully submitted,

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SYNTHESIS AND PHARMACOLOGICAL ACTIVITY OF GUANIDINE AND 2-AMINO 2-IMIDAZOLINE DERIVATIVES

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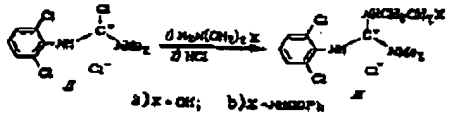
UDC 615.225.2:547.495.9

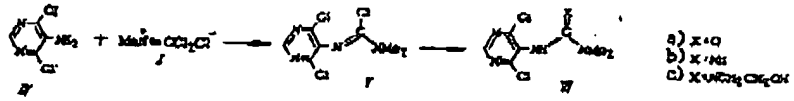
N,N-Dimethyl-N-dichloromethylene-immonium chloride (I) [1, 2] and N,N-dimethyl-N'-(2,6-dichlorophenyl)-C-chloroformamidine hydrochloride (II) [3], which we used in [3] to synthesize the medicinal preparation clofeline (hemiton, catapresan) are readily available starting compounds for the preparation of different derivatives of guanidine and 2-amino-2-imidazoline, which are interesting from the point of view of a search for new hypotensive agents.

In the present work, we synthesized and pharmacologically studied the previously unknown hydrochlorides of N-substituted N'-(2,6-dichlorophenyl)-N",N"-dimethylguanidines (III), obtained from (II) by treatment with 2-aminoethanol and N-benzoylethylenediamine in acetonitrile, according to a method developed by us in [4].



a) X = OH; b) X = NHBz

To obtain guanidine derivatives containing a pyrimidine ring as the substituent, N,N-dimethyl-N'-(4,6-dichloro-5-pyrimidyl)-C-chloroformamidine (V) was synthesized by the reaction of 4,6-dichloro-5-aminopyrimidine (IV) [5] with (I); reaction of (V) with dilute sodium hydroxide, aqueous ammonia and 2-aminoethanol gave N,N-dimethyl-N'-(4,6-dichloro-5-pyrimidyl)-urea (VIa) and substituted guanidines (VIb, c), respectively.



a) X = O
b) X = NH
c) X = NHCH2CH2OH

Besides the "open-ring" analogs of clofeline, it was interesting to obtain for biological studies derivatives of 2-aminoimidazoline containing 2,6-dichlorophenyl and 4,6-dichloropyrimidyl fragments attached to the nitrogen atom of the imidazoline ring. We therefore studied the reaction of substituted guanidines (IIIa) and (VIc) with thionyl chloride. We found that heating (IIIa) and (VIc) with thionyl chloride is accompanied by cyclization and formation of 1-(2,6-dichlorophenyl)- (VII) and 1-(4,6-dichloro-5-pyrimidyl)-2-dimethylaminoimidazolines (VIII). The action of methyl iodide, benzoyl and benzyl chlorides on (VII) yielded the corresponding quaternary salts (IXa-c). By alkaline hydrolysis of (IXa-c), the N-substituted N'-(2,6-dichlorophenyl)-ethylene-ureas (Xa,b) were synthesized. Transition from (Xa) to 1-(2,6-dichlorophenyl)-2-imino-3-methylimidazoline (XI) was carried out by heating (Xa) with phosphorus oxychloride, followed by treatment of the intermediate amidochloride with ammonia.

The structure of compounds obtained was confirmed by the data of IR and UV spectrometry (Table 1).

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Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 15, No. 6, pp. 48-52, June, 1981.
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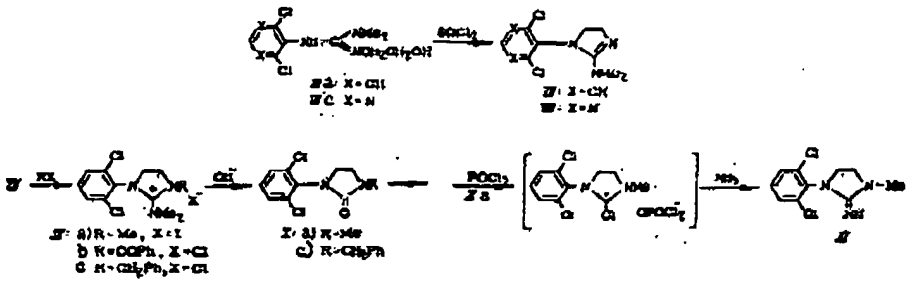
0091-150X/81/1506-0387$07.50

TABLE 1. Yields and Properties of Guanidine and 2-Aminoimidazoline Derivatives (III, V–XI)

Compound	Mp, °C (solvent)	Yield, %	Found, %				Empirical formula	Calculated, %				UV spectrum	IR spectrum, ν, cm^{-1}	
			C	H	Cl	N		C	H	Cl	N	λ_{max}, nm (log ε)	C=N	C=O
IIIa	162—4	80,6	41,86	4,69	23,87	13,36	$C_{11}H_{14}ClN_3O$	49,34	5,12	34,06	13,44	265 (4,02)	1650	—
IIIb	228—30 (methanol–ethyl acetate)	63,7	51,93	5,15	25,61	13,33	$C_{18}H_{21}ClN_4O$	51,99	5,05	25,63	13,48	220 (4,06)	1630,1650	—
V	81—3 (abs. alcohol)	67,6	33,07	2,76	42,14	22,03	$C_7H_7Cl_3N_2$	33,14	2,77	42,01	22,09	244 (4,05)	1650	—
VIa	154—6 (abs. alcohol)	83	35,35	3,38	29,83	24,02	$C_7H_7Cl_3N_2O$	35,74	2,60	30,21	23,83	248 (3,64)	—	1625
VIb	264—8 (ethanol)	74,3	31,60	9,75	39,13	26,00	$C_7H_{10}Cl_2N_2$	31,05	3,70	35,37	25,87	284 (3,73)	1620,1650	—
VIc	14—3 (decomp.)	37,6	36,82	4,72	25,44	25,47	$C_8H_{12}Cl_2N_2O$	38,75	4,68	28,54	25,16	237 (2,97)	1640	—
VII	290—5 (dec.) (isopropanol)	87	44,58	4,62	36,28	14,20	$C_{12}H_{14}Cl_2N_2$	44,62	4,75	35,16	14,26	274 (3,71)	1663	—
VIII	198—201 (ethanol)	45	36,04	4,16	36,01	23,63	$C_9H_{11}Cl_2N_3$	36,42	4,05	35,92	23,81	258 (3,68)	1665	—
IXa	187—8 (acetonitrile–ethyl acetate)	82,2	35,95	3,67	—	19,31	$C_{13}H_{16}ClN_3$	36,00	4,00	—	10,50	295 (4,59)	1640	—
IXb	200—2 (dec.) (acetonitrile–ethyl acetate)	60	54,31	4,67	26,31	10,12	$C_{14}H_{16}ClN_3O$	54,20	4,68	26,72	10,54	262 (4,30)	1635	1708
IXc	207—8 (acetonitrile–ethyl acetate)	51	55,67	5,17	27,64	10,65	$C_{14}H_{18}ClN_3$	55,18	5,20	27,69	10,92	219 (3,74)	1640	—
Xa	135—8 (50% aqueous alcohol)	89	48,89	4,10	29,01	11,21	$C_{20}H_{24}Cl_2N_2O$	48,98	4,08	28,98	11,43	246 (3,38)	—	1700
Xb	105—8 (50% aqueous alcohol)	91	59,72	4,44	22,21	8,67	$C_{26}H_{32}Cl_2N_2O$	59,81	4,36	22,12	8,72	247 (3,48)	—	1692
XI	298—300 (dec.) (isopropanol–ethyl acetate)	86	42,02	4,33	38,08	14,94	$C_{10}H_{11}Cl_3N_2$	42,74	4,28	37,97	14,97	273 (3,77) 281 (3,73)	1655	—



EXPERIMENTAL (PHARMACOLOGICAL)

Compounds (IIIa, b), (VIb, c), (VII), (VIII), (IXa, b, c), and (XI) have elements of slight structural similarity with the hypotensive preparations clofeline, octadine (guanethidine), and esbatal (bethanidine): In their molecule there is a guanidine grouping substituted or included in the ring. The purpose of the pharmacological study was to search for properties characteristic of these preparations: α-adrenomimetic and central hypotensive activity, sympatholytic and ganglio-blocking properties.

We used methods already described in [4]. In the experiments on animals, the compounds were administered intravenously.

In narcotized cats, compound (VIb) in a dose of 5 mg/kg induces a short-term hypertension, which is not changed by the ganglio-blocking agent hexonium (0.5 mg/kg), but is inhibited by the α-adrenolytic preparation phentolamine (1 mg/kg). Hence, (VIb) exhibits an α-adrenomimetic action. Compound (VIb) has no ganglio-blocking properties. In experiments on atropinized vagotomized rats, (VIb) does not lower the systolic frequency, i.e., it does not have a specific central action, characteristic of clofeline.

Compounds (IXa, b, c) in a dose of 2 mg/kg, and (IIIa), (VII), (XI) in a dose of 5 mg/kg cause a decrease in arterial pressure in narcotized cats, due to ganglio-blocking properties, because during hypotension, the nicotine-like preparation cytisine (20 μg/kg) does not increase arterial pressure and does not stimulate respiration. Compounds (IIIb), (VIb, c), and (VIII) do not have ganglio-blocking properties.

At concentrations of up to $1 \cdot 10^{-5}$ g/ml, all the compounds studied do not increase the amplitude of contractions of an isolated spermiduct of a rat, i.e., do not have sympatholytic action.

If we consider the problem of the relationship between the chemical structure of the compounds studied and their pharmacological properties, we note that the derivatives of guanidine and 2-amino-2-imidazoline studied have no action elements characteristic of clofeline, i.e., peripheral α-adrenomimetic properties and the ability, due to central action, to decrease the amount of palpitations in vagotomized rats. Compounds containing the 2,6-dichlorophenyl group, in particular, the quaternary salts (IXa, b, c) have a ganglio-blocking action, but in their activity they are much inferior to known ganglio-blocking agents. Derivatives containing the 4,6-dichloropyrimidine residue (IVb, c, VIII) have no ganglio-blocking properties, although their 2,6-dichloro-phenyl analogs (IIIa, VII) have such properties. The presence in the structure of a guanidine grouping, partially substituted or included in the imidazoline ring, does not impart sympatholytic properties to the compounds studied.

EXPERIMENTAL (CHEMICAL)

The UV spectra of the compounds were run in ethanol on an EPS-3 spectrophotometer, the IR spectra in a crystalline state, in the form of pastes with mineral oil, on Perkin-Elmer-457 (Sweden) and UR-10 (GDR) spectrometers with lithium chloride, sodium chloride, and potassium bromide prisms. The purity of the compounds was controlled chromatographically on Silufol UV-254 plates.

The yields and properties of the compounds studied are listed in Table 1.

Hydrochlorides of N-Substituted N'-(2,6-Dichlorophenyl)-N",N"- dimethylguanidines (IIIa, b). A 9.8-ml (63 mmoles) portion of ethanolamine in 10 ml of acetonitrile is gradually added at 10-15°C to a suspension of 15 g (52 mmoles) of II in 40 ml of acetonitrile. The mixture is left to stand for 16 h at 20°C. The precipitate is filtered, dried, and treated (20°C) with 35 ml of water. The insoluble precipitate is filtered and dried to yield 10.45 g of base (IIIa). An additional amount of (IIIa) is obtained by evaporation of the acetonitrile mother liquor, and treatment of the residue with water. The hydrochloride of (IIIa) is obtained by adding an alcoholic solution of hydrogen chloride to a hot solution of base (IIIa) in ethyl acetate. Compound (IIIb) is synthesized similarly.

N,N-Dimethyl-N'-(4,6-dichloro-5-pyrimidyl)-O-chloroformamidine (V). A solution of 4.45 g (27 mmoles) of (IV) in 70 ml of methylene chloride is added at the boiling point to a suspension of 4.43 g (27 mmoles) of (I) in 30 ml of dry methylene chloride, and the mixture is boiled for another hour. The reaction mixture is evaporated to dryness, and the residue crystallized from absolute alcohol to yield (V).

N,N-Dimethyl-N'-(4,6-dichloro-5-pyrimidyl)-urea (VIa). A 2.53-g (0.01 mole) portion of (V) in 10 ml of sodium hydrochloride is heated at 50°C for 1.5 h. The precipitate is filtered, washed with water and dried to yield (VIa).

Hydrochlorides of N-Substituted N'-(4,6-dichloro-5-pyrimidyl)-N", N"- dimethylguanidines (VI, b, c). A 1.27-g (5 mmoles) portion of (V) in 10 ml of 25% aqueous ammonia is heated at 50°C for 1.5 h. When cool, the precipitate is filtered, washed with water, and dried to yield base (VIb). The hydrochloride of (VIb) is obtained in the same way as (III). Compound (VIc) is synthesized similarly.

Hydrochlorides of 1-Substituted 2-dimethylamino-2-imidazolines (VII, VIII). A 3.25-g (0.01 mole) portion of (IIIa) is boiled for 1 h with 25 ml of thionyl chloride. The reaction mixture is evaporated to dryness, and the residue of thionyl chloride removed by distillation with chloroform. The reaction mixture is treated at 10-15°C with 15 ml of water, made alkaline with 40% sodium hydroxide solution to pH 10.0, and extracted with ethyl acetate. The extract is clarified with activated charcoal, and evaporated to 15-20 ml, and the hydrochloride of (VII) is isolated by adding an alcoholic solution of hydrogen chloride. Compound (VIII) is synthesized similarly.

Quaternary Salts of 1-(2,6-Dichlorophenyl)-2-dimethylamino-2-imidazoline (IXa-c). A mixture of 12.9 g (0.05 mole) of (VII) and 3.1 ml (0.05 mole) of methyl iodide in 50 ml of acetonitrile is heated at 40-50°C for 1.5 h. The mixture is cooled to 20°C, and the reaction mixture is treated with 100 ml of ethyl acetate. The precipitate is filtered to yield (IXa). Compounds (IXb, c) were synthesized similarly.

N-Substituted N'-(2,6-Dichlorophenyl)-ethylene-ureas (Xa, b). A 11.45-g (29 mmoles) portion of (IXa) in 57 ml (57 mmoles) of 1 N sodium hydroxide is boiled for 2 h. The precipitate is filtered, washed with water, and dried to yield (Xa). Compound (Xb) is similarly obtained from (IXc).

Hydrochloride of 1-(2,6-Dichlorophenyl)-2-amino-3-methylimidazoline (XI). A 5.1-g (0.02 mole) portion of (Xa) is boiled for 4.5 h with 20 ml of phosphorus oxychloride. The reaction mixture is evaporated *in vacuo* and the residue treated with 15 ml of toluene. The precipitate is filtered and washed with toluene and dry ether. The precipitate is added in portions at 0-5°C to 40 ml of acetonitrile saturated with ammonia, and the reaction mixture is held for 2 h at 20°C. The precipitate is filtered, washed with acetonitrile, dried, treated with 20 ml of water, made alkaline to pH 10, and extracted with chloroform. After removal of solvent, the residue is dissolved in 30 ml of ethyl acetate, and hydrochloride of (XI) is isolated by adding an alcoholic solution of hydrogen chloride.

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CYCLIZATION OF N,N-DIMETHYL-N'-(DICYANOVINYL)-C-CHLOROFORMAMIDINES TO PYRIMIDINES

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Ukrainskii Khimicheskii Zhurnal,
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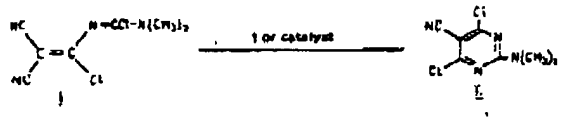
The ability of N,N-dimethyl-N'-(dicyanovinyl)-C-chloroformamidines to cyclize to 4-chloro-2-dimethylamino-5-cyanopyrimidines upon reaction of a series of nucleophilic and electrophilic catalysts was observed. It was established that N,N-dimethyl-N'-(dicyanovinyl)-C-chloroformamidines react with triethyl phosphite by an Arbuzov rearrangement scheme with substitution of one chlorine atom by a phosphoryl group and formation of phosphorylated formamidines, which cyclize to phosphorylated pyrimidines. Substitution of both chlorine atoms by phosphoryl groups occurs upon reaction of triethyl phosphite and 2-dimethylamino-5-cyano-4,6-dichloropyrimidine.

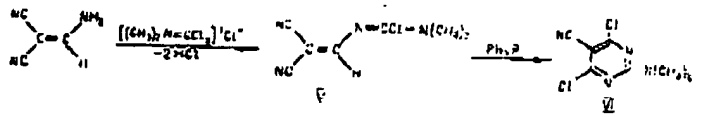
Studying the properties of N,N-dimethyl-N'-(1-chloro-2,2-dicyanovinyl)-C-chloroformamidine (I), obtained by us earlier from sodium tricyanomethanide and N,N-dimethyldichloromethaniminium chloride [1], we observed its ability to cyclize easily with formation of a pyrimidine ring. Cyclization of formamidine I to 4,6-dichloro-2-dimethylamino-5-cyanopyrimidine (II) already occurs upon heating above the melting point (130-150°) and also in the presence of catalysts - nucleophilic and electrophilic agents. Cyclization is caused by heating benzene solutions of formamidine I in the presence of catalytic amounts of triethylamine and triphenylphosphine, aluminum chloride, chlorine, N,N-dimethylchloromethaniminium chloride, and phosphorus pentachloride:



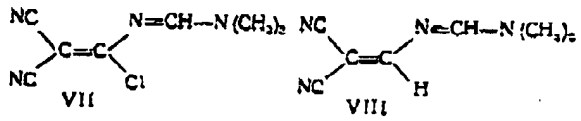
Conclusions concerning the pyrimidine structure of isomerization products of formamidine I were drawn on the basis of a comparison of spectral characteristics of compounds I and II. The IR spectrum of pyrimidine II contains one absorption band of the C ≡ N group at 2240 cm^{-1}, while in the spectrum of formamidine I absorption of the C ≡ N group as a doublet at 2220-2240 cm^{-1}. The absorption picture in the region of 1500-1650 cm^{-1} for compounds I and II also has significant differences. In PMR spectra of a benzene solution of pyrimidine II protons of the dimethylamino group appear as a singlet with σ = 2.07 ppm, while for formamidine I they appear as two signals at 1.75 and 1.85 ppm. UV spectra of pyrimidine II contain two absorption maxima at 278 and 330 nm, characteristic for the pyrimidine ring [2].

The reaction of pyrimidine II with aniline occurs with substitution of both chlorine atoms by a phenylamino group and formation of compound III, which in melting point and spectral characteristics also differs significantly from the acyclic isomer IV, which we obtained earlier [1]:

Formation of the pyrimidine structure during isomerization of formamidine I is confirmed by the fact that N,N-dimethyl-2,2-dicyanovinyl-6-chloroformamidine (V) cyclizes easily upon reaction with triphenylphosphine to the known [3] 4-chloro-2-dimethylamino-5-cyanopyrimidine (VI). Formamidine V was obtained from 1-amin-2,2-dicyanoethylene and N,N-dimethyldichloromethaniminium chloride:

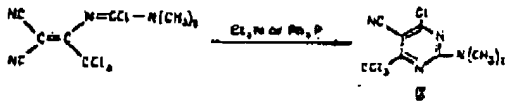


N-(2,2-Dimethyl-N'-(1-chloro-2,2-dicyanovinyl)formamidine (VII) and N,N-dimethyl-2,2-dicyanovinylformamidine (VIII), in which a chlorine in the formamidine fragment is absent, do not isomerize under the same conditions:

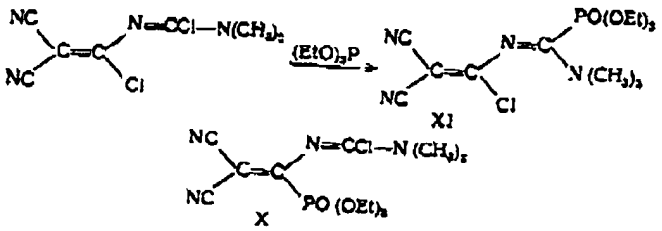


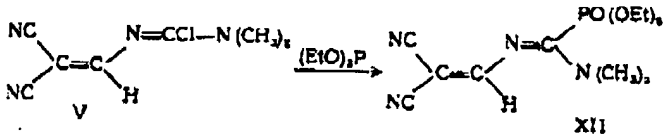
Thus, cyclization to pyrimidines is only possible for cyanovinyl-C-chloroformamidines. This also corresponds to data on cyclization of N,N-dialkyl-N'-2-carbethoxyvinyl-C-chloroformamidines to oxazine derivatives [4]; such formamidines without chlorine atoms in the formamidine fragment do not cyclize.

N,N-Dimethyl-N'-(1-trichloromethyl-2,2-dicyanovinyl)-C-chloroformamidine in the presence of triethylamine or triphenylphosphine, like formamidines I and II, easily isomerizes to 4-chloro-6-trichloromethyl-2-dimethylamino-5-cyanopyrimidine (IX):

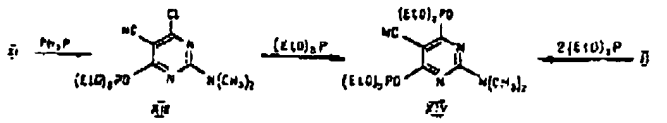


In contrast to triphenylphosphine, triethyl phosphite does not cause isomerization of formamidine (I) to pyrimidine (II), but reacts with it by the scheme of the Arbuzov reaction with substitution of only one of the chlorine atoms on the phosphoryl group. The remaining chlorine atom cannot be substituted by a second phosphoryl group even upon heating formamidine (I) in excess triethyl phosphite and also without solvent. It was logical to propose that the reaction with triethyl phosphite occurs at the dicyanovinyl fragment and compound X is formed, since it is known that acceptor cyano groups facilitate nucleophilic substitution of the vinyl halogen [5]. However, N,N-dimethyl-N'-(1-chloro-2,2-dicyanovinyl)formamidine does not react with triethyl phosphite and N,N-dimethyl-N'-(1,2,2-dicyanovinyl)-C-chloroformamidine reacts with triethyl phosphite with formation of compound XII. On this basis it should be considered that the reaction of formamidine (I) with triethyl phosphite occurs at the formamidine fragment and N,N-dimethyl-N'-(1-chloro-2,2-dicyanovinyl)-C-diethoxyphosphonylformamidine (XI), and not its isomer X is formed. The spectral characteristics of compounds XI and XII correspond to the proposed structures:





Upon heating in the presence of a catalytic amount of triphenylphosphine the phosphorus-containing formamidine (XI) isomerizes to 4-chloro-2-dimethylamino-5-cyano-6-diethoxyphosphonylpyrimidine (XIII), which upon reaction with triethyl phosphite gives 2-dimethylamino-5-cyano-4,6-bis(diethoxyphosphonyl)pyrimidine (XIV). The latter was also obtained directly from dichloropyrimidine (II) and two moles of triethyl phosphite; subsequent substitution of chlorine atoms by phosphoryl groups could not be carried out.



Cyclization of the C-phosphoryl derivative of formamidine XI is evidently due to migration of the phosphoryl group, as a result of the instability of the C-P bond in the formamidine fragment, structurally similar to the acyl phosphonites RCO—P(O)(OR)$_2$ (comp. [6]).

IR spectra of compounds were taken on a Specord IR-71 instrument in KBr tablets and UV spectra were obtained on a Specord UV-VIS spectrophotometer instrument in alcoholic solutions. PMR spectra were recorded on a Tesla BS-487 B spectrometer (80 MHz) at room temperature in benzene solutions with HMDS as the external standard. The purity of compounds was controlled on UV-254 silufol with chloroform:ethyl acetate (1:1) as the eluent.

N,N-Dimethyl-N'-(1-chloro-2,2-dicyanovinyl)-C-chloroformamidine (I) and N,N-dimethyl-N'-(1-chloro-2,2-dicyanovinyl)formamidine (VII) were obtained by the method of [1]; N,N-dimethyl-N'-(1-trichloromethyl)-2,2-dicyanovinyl-C-chloroformamidine was obtained by the method of [4].

N,N-Dimethyl-N'-dicyanovinylformamidine (VIII). A mixture of 0.01 mole of 1,1-dicyanovinyl-2-aminoethylene, 0.01 mole of N,N-dimethylchloromethaniminium chloride, and 30 ml of chloroform was stirred for 2 hr at 20-25° and then boiled for 2 hr until separation of hydrogen chloride ceased. The solvent was distilled and the residue was crystallized from alcohol. Yield 64%, MP 222-224°. IR spectrum: 2290, 2210, 1640, 1580, 1460, 1360, 1300, 1260, 1110, 1040, 880 cm^{-1}. UV spectrum: λ_{max} = 260 nm.

Found, %: C 55.97; H 4.81; N 37.12. $C_7H_8N_4$. Calculated, %: C 56.76; H 5.4; N 37.83.

N,N-Dimethyl-N'-(dicyanovinyl)-C-chloroformamidine (VII). A mixture of 0.01 mole of 1,1-dicyanovinyl-2-aminoethylene, 0.01 mole of N,N-dimethyldichloromethaniminium chloride, and 30 ml of chloroform was boiled for 3 hr until separation of hydrogen chloride ceased. The solvent was distilled and the residue was treated with hexane and crystallized from a benzene-hexane (5:1) mixture. Yield 76%. Mp 181-182°. IR spectrum: 2220, 1640, 1560, 1420, 1380, 1280, 1190, 1080, 910, 880 cm^{-1}. UV spectrum: λ_{max} = 275 nm.

Found, %: C 47.10; H 5.75; N 29.97; Cl 19.17. $C_7H_7ClN_4$. Calculated, %: C 46.04; H 6.03; N 30.68; Cl 19.43.

Cyclization of N,N-dimethyl-N'-(1-chloro-2,2-dicyanovinyl)-C-chloroformamidine (I). 4,6-Dichloro-2-dimethylamino-5-cyanopyrimidine (II). A. 0.01 mole of N,N-dimethyl-N'-(1-chloro-2,2-dicyanovinyl)-C-chloroformamidine was heated for 30 min at 130°. The melt foamed and solidified. The mixture was cooled to 20-25°, pulverized, and crystallized from benzene or hexane. Yield 86%. Mp 221-222°. IR spectrum: 2240, 1640, 1480, 1420, 1410, 1350, 1210, 1140, 1080, 1020, 850, 800 cm^{-1}. UV spectrum: λ_{max} = 278, 330 (shoulder) nm. PMR spectrum: 2.87 ppm.

Found, %: C 38.79; H 2.81; Cl 32.79; N 25.58. $C_7H_6Cl_2N_4$. Calculated, %: C 38.73; H 2.78; Cl 32.66; N 25.81.

d. To a solution of 0.01 mole of compound I in 20 ml of benzene was added 1-2 drops of triethylamine and the mixture was boiled for 30 min. The solvent was evaporated by one-half and cooled to 15°; the precipitate was filtered and dried. Yield 80%. A mixed sample with the sample, obtained by method A, did not give a melting point depression. IR and UV spectra were identical.

C. A mixture of 0.025 mole of compound I, 0.001 mole of triphenylphosphine, and 30 ml of benzene was boiled for 3 hr. The solvent was distilled and the residue was washed twice with 5 ml of cold benzene (10°) and crystallized from benzene. Yield 95%. Identification was the same as indicated in method B.

D. Into a solution of 0.02 mole of compound I in benzene was passed dry hydrogen chloride for 30 min. The solvent was evaporated and the residue was crystallized from hexane. Yield 69%. Identification was in accordance with method B.

E. Into a solution of 0.01 mole of compound I in 20 ml of methylene chloride was passed chlorine in a slow current for 20 min. The solvent was evaporated and the residue was crystallized from benzene or hexane. Yield 67%. It was identified as in method B.

F. Into a solution of 0.01 mole of compound I in 20 ml of methylene chloride was slowly passed chlorine for 20 min. The solvent was evaporated and the residue was crystallized from benzene. Yield 67%. It was identified as in method B.

G. 0.01 mole of compound I, 0.005 mole of N,N-dimethyldichloromethaniminium chloride, and 30 ml of chloroform were boiled for 3 hr. The solvent was evaporated and the residue was crystallized from hexane. Yield 73%. It was identified by method B.

Cyclization under the effect of PCl_5 or $AlCl_3$ proceeded analogously.

Cyclization of N,N-dimethyl-N'-(dicyanovinyl)-C-chloroformamidine (V). 4-Chloro-2-dimethylamino-5-cyanopyrimidine (VI). A mixture of 0.01 mole of compound I, 0.001 mole of triphenylphosphine, and 30 ml of benzene was boiled for 3 hr. The solvent was distilled and the residue was washed with 5 ml of cold benzene (10°) and crystallized from benzene. Yield 77%. It was identified from physical constants with the compound, obtained by the method of [3].

N-N-Dimethyl-N'-(1-chloro-2,2-dicyanovinyl)-C-diethoxyphosphonylformamidine (XI). A mixture of 0.01 mole of compound I and 0.01 mole of triethyl phosphite was maintained at 70-75° for 2 hr until the separation of ethyl chloride ceased. The yield of the latter was 90%. The mixture was cooled to 20-25° and the crystalline residue was treated with 5 ml of cold benzene (10°) and was crystallized from hexane. Yield 63%. Mp 86-87°. IR spectrum: 2220, 1640, 1580, 1420, 1280, 1160, 1060, 1040, 990, 910, 820 cm^{-1}. UV spectrum λ_{max} = 285, 340 nm. PMR spectrum: 2.28, 1.78 ppm.

Found, %: C 41.44; H 4.62; N 17.60; P 10.06. $C_{11}H_{16}ClN_4O_3P$. Calculated, %: C 41.45; H 5.06; N 17.58; P 9.71.

Cyclization of N,N-dimethyl-N'-(1-chloro-2,2-dicyanovinyl)-C-diethoxyphosphonylformamidine (XI). 4-Chloro-2-dimethylamino-5-cyano-6-diethoxyphosphonylpyrimidine (XIII). 0.01 mole of compound XI and 0.001 mole of triphenylphosphine were maintained at 120° for 2 hr. The mixture was cooled to 20-25°, washed 2 times with 10 ml of cold benzene (10°), and crystallized from a benzene-hexane mixture. Yield 62%. Mp 130° (with decomposition). IR spectrum: 2820, 2280, 1600, 1540, 1460, 1420, 1410, 1350, 1300, 1220, 1110, 1060, 950, 740, 710 cm^{-1}. UV spectrum: λ_{max} = 230, 320 nm.

Found, %: P 9.80. $C_{11}H_{16}ClN_4O_3$. Calculated, %: Cl 11.12; P 9.71.

2-Dimethylamino-4,6-diethoxyphosphonyl-5-cyanopyrimidine (XIV). A mixture of 0.02 mole of 2-dimethylamino-4,6-dichloro-5-cyanopyrimidine and 0.05 mole of triethyl phosphite was maintained at 100° for 2 hr until separation of ethyl chloride ceased. The mixture was cooled to 20-25° and the residue was recrystallized from chloroform. Yield 80%. MP

175-178° (with decomposition). IR spectrum: 2240, 1690, 1660, 1500, 1480, 1440, 1410, 1360, 1250, 1050, 960 cm^{-1}. UV spectrum: λ_{max} = 250, 330 (shoulder) nm.

Found, %: C 48.10; H 4.91; N 11.52; P. 13.12. $C_{19}H_{26}I_4O_5P_2$. Calculated, %: C 28.70; H 5.59; N 11.96; P. 13.22.

2-Dimethylamino-4,6-phenylamino-5-cyanopyrimidine. 0.01 mole of 2-dimethylamino-4,6-dichloro-5-cyanopyrimidine was dissolved in 20 ml of tetrahydrofuran and 0.04 mole of aniline in 10 ml of tetrahydrofuran was added. The mixture was boiled with stirring for 5 hr and cooled to 20°. The aniline hydrochloride was filtered and the filtrate was evaporated. The residue was crystallized from methanol. Yield 65%. Mp 195-197° (with decomposition).

Found, %: C 69.28; H 5.20; N 25.52. $C_{19}H_{17}N_6$. Calculated, %: C 69.71; H 5.24; N 25.59.

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